RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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Cognitive Strategy Reduces Craving by Altering Brain Activity

Brain imaging reveals changes when smokers focus on long-term consequences of their tobacco use.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Addiction makes it difficult for people to look beyond immediate gratification to the longer term consequences of their actions. Accordingly, patients in drug abuse treatment are often coached to make and rehearse mental associations between situations that trigger drug cravings and the problems that are likely to ensue from succumbing to them. The cognitive behavioral programs that incorporate this strategy generally are effective, but researchers have shed little light on the neurological basis for their efficacy—until now.

In a study led by Dr. Kevin N. Ochsner of the Social Cognitive Neuroscience Laboratory at Columbia University, smokers reported milder cigarette cravings when they thought about smoking's harmful effects while viewing smoking cues than when they focused on its pleasures. Brain imaging correlated the reductions in craving with altered activity levels in regions associated with emotional regulation and reward.

MENTAL ADJUSTMENT ALTERS BRAIN ACTIVITY

Dr. Ochsner and colleagues recruited smokers as study subjects because smoking accounts for more illness and death than any other addiction. To gain insight on the smokers' ability to regulate cravings in general, the team also investigated their responses to cues for high-fat food.

The participants were 21 men and women who had smoked for 10 years, on average, and were not trying to quit. In preparation for the study, the participants practiced turning their thoughts to rewarding effects of cigarettes or high-fat food consumption when given the instruction "NOW" and to negative effects when given the instruction "LATER." In the study itself, the researchers gave each participant 100 such instructions, in random order, each

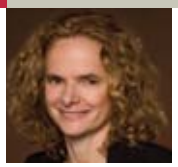
[*Continued on page 6*]

Last Print Issue

This is the final print edition of *NIDA Notes*. The new all-Web newsletter is up and running at *www.drugabuse.gov/NIDANotes/*. Access to the site is free, and e-mail subscribers will receive bimonthly updates with links to new Web content and notices of special news and events. Don't miss out! If you are not an e-mail subscriber to *NIDA Notes*, or if you need to update your e-mail address, please enter your subscriber information on *www.nidanotes.org/pages/AddEmail.aspx*, or fill out and return the postcard from this issue's wraparound cover.

ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*



Research Focuses on Groups With High Smoking Rates

In the 60 years since public health researchers first established that cigarettes cause lung cancer, the percentage of Americans who smoke has dropped from 40 to 20. Yet despite all we now know about tobacco's disabling and deadly effects, 46 million Americans still smoke. The figure attests to the tenacity of the addiction and the critical need for more effective prevention and treatment interventions.

A large portion of today's smokers belong to subpopulations that have not benefited as much as the general population from health information and clinical advances. People with psychiatric disorders, for example, smoke at roughly twice the average rate of the population as a whole. Smoking is particularly prevalent—ranging from about 50 to 90 percent—among individuals with schizophrenia, bipolar disorder, depression, and substance use disorders. High school dropouts are about three times as likely to smoke as those with college degrees. Of particular concern are the rates and intensity with which pregnant women who have dropped out of high school smoke, thereby incurring health risks for their children as well as themselves. Ethnicity influences smoking, too. An estimated 32 percent of Native American adults smoke, compared with 22 percent of white adults, according to 2008 data from the Centers for Disease Control and Prevention.

NIDA-supported researchers are working to develop highly effective treatments for every smoker. Some of their efforts on behalf of groups with elevated smoking rates have shown:

- Bupropion can help people with schizophrenia quit (*NIDA Notes*, Volume 20, Number 5, page 7);
- Smokers with depression respond well when motivational feedback from a computer program precedes medication and behavioral therapy (*NIDA Notes*, Volume 21, Number 3, page 1);
- Low-income pregnant women show improved quit rates and increased fetal growth when abstinence is rewarded with vouchers exchangeable for retail items (*NIDA Notes*, Volume 23, Number 1, page 10).

The Institute currently supports research to improve treatment outcomes for smokers with posttraumatic stress and other anxiety disorders, schizophrenia, and attention deficit hyperactivity disorder.

The impressive reduction in smoking rates over the past half-century has been incremental, propelled by public health interventions, therapeutic advances, and educational programs. The challenge now is to extend that progress to the hardest-to-reach individuals and groups and those with the most severe smoking addictions. To that end, NIDA continues its efforts to fill research gaps, translate knowledge into new treatments, and expand access to effective, research-based prevention interventions and cessation therapies. ■

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Alleviation of Posttraumatic Stress Disorder May Improve Addiction Treatment

In a recent NIDA-funded study, women responded better to substance abuse treatment after their posttraumatic stress disorder (PTSD) symptoms improved, but reductions in substance abuse did not ease PTSD severity. The 353 participants in the 6-week treatment were patients in seven community-based substance abuse treatment programs in NIDA's Clinical Trials Network. The women received their programs' standard drug treatments, plus 12 group sessions of either Seeking Safety—a cognitive-behavioral therapy with components addressing both trauma and substance abuse—or Women's Health Education, which does not specifically address either problem. The study found that the two added therapies had similar effects.

When the data from the two treatment arms were combined in a secondary study, PTSD severity reductions were associated with subsequent substance use disorder improvement, but there was minimal evidence that substance use reduction improved PTSD symptoms. Lead researcher Dr. Denise Hien of City University of New York and Columbia University says the findings indicate that people with trauma self-medicate with substances of abuse. She suggests that clinicians reconsider the common practice of requiring patients to attain abstinence before treating their trauma symptoms.

> American Journal of Psychiatry 167(1):95–101, 2010.

Desire to Smoke Subsides, But Cigarette Cues Retain Power

A study by Drs. Gillinder Bedi and Harriet de Wit of the University of Chicago and Drs. Kenzie Preston, David Epstein, and Stephen Heishman of the NIDA Intramural Research Program provided initial evidence that drug-dependent humans can experience "incubation" of cue-induced craving. The phenomenon—an increasing susceptibility to drug cues during the first months of abstinence—has been documented repeatedly in animals. The issue has important clinical implications, suggesting that cues may continue to act as a potent trigger for relapse well past the initial period of withdrawal.

The 86 participants in the study were daily smokers who were not seeking treatment and were paid to quit for 7, 14, or 35 days. They came to the laboratory daily for tests to confirm abstinence, and the researchers measured their craving responses to cues on the last day of their participation. One group also participated in repeated cue tests on days 7, 14, and 35. The cues consisted of holding a lit cigarette and looking at photos of cigarettes, and participants rated their craving before and after cue exposure.

The cue-induced craving was roughly twice as strong after 35 days of abstinence than it was after 1 week. Moreover, the craving increased over this period even though the smokers' urges to light up in the absence of cues steadily weakened, dropping by more than 25 percent over 5 weeks.

> Biological Psychiatry 69(7):708–711, 2011.

High Rates of Job Leaving Among Addiction Counselors

In the course of a single year, one in three substance abuse counselors and about one in four clinical supervisors in a national sample of 27 treatment organizations left their jobs, report Dr. Lillian T. Eby and colleagues at the University of Georgia.

Of the 739 full-time counselors on the organizations' rosters in 2008, 245 (33 percent) left within a year, 184 (75.1 percent) voluntarily and 55 (22.4 percent) involuntarily. (Six counselors could not be tracked.) Of 188 supervisors, 44 (23 percent) left, 27 (61.4 percent) of their own accord and 14 (31.8 percent) otherwise—7 of them because of program closure and layoffs. (Three supervisors could not be tracked.)

In interviews with 80 former employees, the most common reason given for leaving voluntarily was to go to a new job or take advantage of an opportunity. Less than 5 percent of counselors and less than 3 percent of supervisors said they had left their jobs because of dissatisfaction or to seek higher pay.

Dr. Eby and colleagues say that their data point to a problem in the substance abuse treatment field. Not only were voluntary annual turnover rates in the 27 organizations markedly higher than the average throughout health care and social assistance professions—which the Bureau of Labor Statistics puts at about 20 percent—but 36 percent of counselors who quit their jobs left the field altogether. Other research has indicated that high rates of counselor turnover may increase costs, decrease efficiency and morale, and adversely influence patient outcomes. The Georgia researchers suggest that voluntary turnover may be reduced by interventions that enhance the quality of professional experience and decrease workplace stress, and that better professional preparation may decrease involuntary turnover.

> Journal of Substance Abuse Treatment 39(3):264–271, 2010.

Women and Sex/Gender Differences Research Program

BY LORI WHITTEN,
NIDA Notes Staff Writer

Since its inception, NIDA has sponsored research on issues related to women. Beginning with an early focus on the effects of drug use on pregnant women and the children they bear, the Institute soon expanded its interest to sponsor research into women's specific addiction risk factors and treatment needs. When the HIV/AIDS epidemic emerged in the 1980s, NIDA responded with funding for projects on gender-specific risk factors for infection and on the impact of drug abuse on HIV transmission between mother and newborn and the subsequent health of both.

In 1995, NIDA formally established the Women and Sex/Gender Differences Research Program with the objective of achieving a comprehensive understanding of addiction and optimally effective prevention and treatment interventions for both men and women. The Program works with NIDA's Divisions to integrate the study of male-female differences in drug and treatment responses into all areas of NIDA-sponsored research. "Without information on sex and gender effects, researchers may draw incorrect conclusions about the underlying causes of addiction and best ways to prevent and treat addiction in both men and women," says Dr. Cora Lee Wetherington, the Program's Research Coordinator.

STRATEGIC AND DISSEMINATION ACTIVITIES

Dr. Wetherington and Program Deputy Research Coordinator Dr. Samia Noursi lead the Women and Sex/Gender Differences Research Group (WGRG). This group regularly convenes scientists from throughout NIDA to discuss the state of scientific knowledge, new findings, and as yet unanswered questions. WGRG members draw on these exchanges to infuse issues of women and sex/gender differences into all types of Institute research, from animal models to intervention trials. For example, WGRG members helped plan NIDA's recent research initiatives on gender differences in prescription drug abuse, the efficacy of addiction treatments, and substance abuse among members of the military and their families.

The WGRG also organizes and sponsors—often in collaboration with other groups—symposia, seminars, and Webinars to provide addiction researchers, clinicians, and program administrators with the latest information on the influence of sex and gender on drug abuse. Recent topics of these dissemination activities have included interventions to reduce smoking among pregnant women, HIV prevention among women who abuse drugs, and the potential impact of sex-related neurobiological differences on addiction.

To encourage young researchers to get involved in addiction research on sex and gender differences, the Program has established a dissertation award program for outstanding studies in this area and provides travel awards to the annual meeting of the College on Problems of Drug Dependence.

The Program has partnered with the National Institute on Alcohol Abuse and Alcoholism in issuing the funding opportunity announcement, "Women and Sex/

HEIGHTENED BRAIN RESPONSE TO CIGARETTE CUES AMONG WOMEN After exposure to cigarette cues, female smokers showed heightened activity in several brain regions—including areas of the reward pathway—compared with male smokers, Dr. Teresa Franklin and colleagues at the University of Pennsylvania have demonstrated. The top three functional magnetic resonance images show the locations where females have greater activity, and the lower three show the locations of heightened activity in males. The largest differences appear white/yellow, and more moderate differences appear orange.

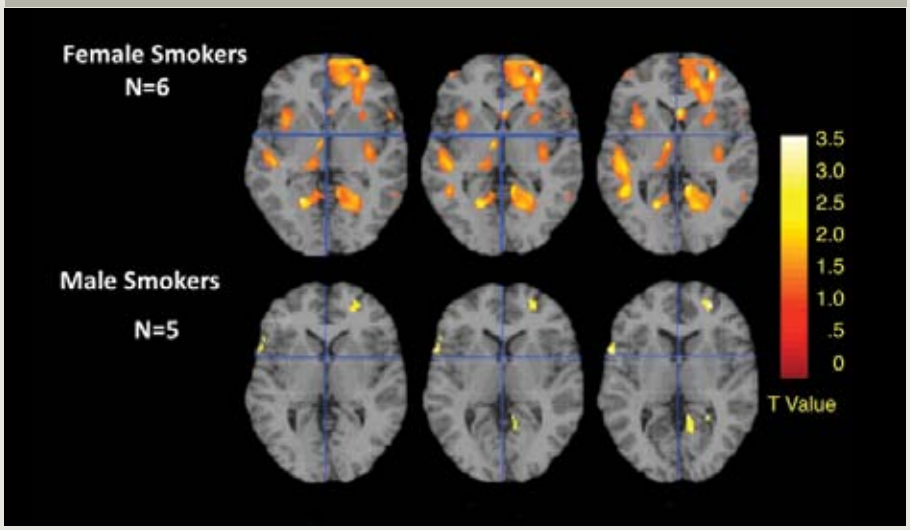


Image courtesy of Teresa Franklin, Jason Gray, John Listerud, John Monterosso, Charles P. O'Brien, and Anna Rose Childress.

Gender Differences in Drug and Alcohol Abuse/Dependence" (*http://grants.nih.gov/grants/guide/pa-files/PA-11-047.html*). The Program has long-standing collaborations with the National Institutes of Health (NIH) Office of Research on Women's Health, with which NIDA co-funds three center grants and mentoring for junior faculty to develop research careers focusing on women and sex/gender differences in drug abuse.

SEX AND GENDER IN THE CLINIC...

"Clinical studies that examine outcomes separately for men and women can help determine whether treatments have differential effectiveness or distinct side effects in the two genders," says Dr. Wetherington. The Program works closely with NIDA's Clinical Trials Network (CTN), helping investigators formulate hypotheses and design protocols that take into account sex- and gender-related differences in responses to treatment. CTN studies, which are conducted in community-based treatment facilities, have shown that gender-specific programs to teach substance-abusing men and women safe-sex skills outperform standard care in reducing risky behaviors (see "Intensive Interventions Reduce Risky Sexual Behaviors," *NIDA Notes,* Volume 23, Number 5, page 10).

The Program takes the lead in promoting NIDA clinical research on drug abuse among pregnant women and its effects on their children. The value of such studies is exemplified by recent findings that interventions that bridge prenatal care and help build parenting skills improve treatment outcomes for both mother and child (see "Home Visits by Nurses to Low-Income First-Time Mothers Yield Enduring Benefits," this issue, page 12) and that treating addicted pregnant women with buprenorphine rather than methadone can lead to shorter hospital stays for their newborns and less need to give neonates methadone for opioid withdrawal.

Many Differences

NIDA research indicates that optimal treatment for all drug abusers must take into account male-female differences in:

- Responses to drugs in some brain areas
- Risk and protective factors for drug abuse
- Reasons for abusing prescription drugs in young adulthood
- Benefits obtained from certain treatments
- Reasons for dropping out of treatment and relapsing
- Outcomes affected by prenatal drug exposure

Among the Program's clinical foci, the issue of sex-specific responses to medication interventions addresses a historically understudied area. For many years, researchers omitted women from clinical trials to avoid the difficult challenge of assessing possible effects of female hormones and menstrual cycles on the study results. This situation has eased since NIH mandated the inclusion of women in all NIH-funded clinical trials in the mid-1990s. NIDA-supported findings underline the importance of this mandate: We now know, for example, that women have a harder time quitting smoking than men and benefit less from nicotine replacement therapy.

... AND IN BASIC RESEARCH

The Program promotes laboratory research to seek neurobiological explanations for differences in drug and treatment responses observed between men and women and to reveal differences between male and female animal behaviors that have potential relevance for people. Among potentially far-reaching findings in the latter line, recent studies have shown that female rats learn to self-administer several types of drugs of abuse more quickly than males, consume more of the drugs, and demonstrate greater reinforcement from them. "This animal model and human laboratory research can suggest prevention and treatment strategies that are gender-based or have gender-based components," says Dr. Wetherington.

Although hormones are not the only reason a drug or medication might affect men and women differently, the question of hormonal influences on drug responses may be critical for the addiction field. "Scientists know that ovarian hormones influence neurotransmitters that are associated with addiction, and NIDA basic researchers have shown that these hormones affect drug self-administration, the motivational properties of drugs, and the neural processes underlying addiction. This is why it is important for NIDA's research with animal models to include females and examine the role of ovarian hormones on outcomes," Dr. Wetherington says.

The Program is hoping to take full advantage of the many powerful new research tools and techniques that are available for the identification and elucidation of gender differences. Dr. Wetherington says, "New imaging modalities, molecular biology, and genetics are making great contributions to our understanding of addiction. We need to infuse the study of sex differences in those and other fields." ■

COGNITIVE STRATEGY

[*Continued from page 1*]

followed by a 6-second exposure to a screen image of either cigarettes or food. Then, after a 3-second delay with the screen blank, the participant reported how much he or she desired to smoke or eat, on a scale of 1 (not at all) to 5 (very much).

The power of thinking about negative effects proved to be considerable. The participants reported 34 percent less intense urges to smoke and 30 percent less intense food cravings after the LATER instruction compared with the NOW instruction.

Brain scans taken during the experiment showed how concentrating on long-term negative consequences alters brain activity to reduce craving. Functional magnetic resonance imaging (fMRI) of the participants' whole brain revealed increased activity levels in areas—the dorsomedial, dorsolateral, and ventrolateral regions of the prefrontal cortex (PFC)—that support cognitive control functions, such as focusing, shifting attention, and controlling emotions. Activity decreased in regions that previous studies have linked with craving; these areas include the ventral striatum and ventral tegmental area, which are parts of the reward circuit; the amygdala; and the subgenual cingulate. Individual participants who reported larger reductions in craving exhibited these changes to a more marked degree. A specialized mediation analysis of the images found that the increase in PFC activity drove the decrease in ventral striatum activity, which, in turn, fully accounted for the reduction in craving.

"These results show that a craving-control technique from behavioral treatment influences a particular brain circuit, just as medications affect other pathways," says Dr. Steven Grant of NIDA's Division of Clinical Neuroscience and Behavioral Research.

The researchers noted that the study participants reduced their smoking and food cravings to the same extent, even though smoking cravings were initially more intense. This finding suggests that calling undesirable consequences to mind has potential to help people overcome a variety of unhealthy urges.

HEALING PERSPECTIVES

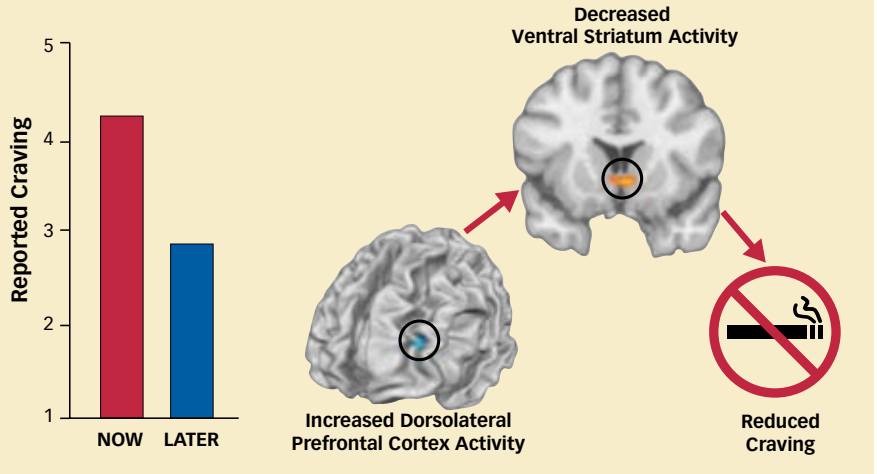
"Cognitive reappraisal—mentally changing the meaning of an event or object to lessen its emotional impact and therefore alter the behaviors it triggers—is a strategy that helps a variety of problems," says Dr. Ochsner. Cognitive-behavioral therapists train patients to use this approach, among others, to cope with negative emotions, stress, and substance cravings. Dr. Ochsner says, "People may not realize that they can control cravings or emotions using cognitive strategies—for example, thinking of negative consequences and distracting and distancing oneself—but patients can learn these techniques and then must continue to apply them over time."

Dr. Ochsner says there is broad scientific interest in the neurobiological mechanisms underlying cognitive control over thoughts and emotions that promote unhealthy behaviors. Such studies generally find that although there is some overlap in the regions of the PFC engaged when people exert cognitive control, different areas seem to support different strategies for the regulation of emotional responses.

"The mediation analysis that Dr. Ochsner and colleagues conducted is unique among imaging studies and is a particular strength of this research," says Dr. Grant. "Because the researchers examined the interaction of brain regions, the results provide a perspective on the neural circuits involved in cognitive control of craving."

Dr. Grant suggests two important next steps in this area of research: identifying why some people have more problems than others in controlling the desire for cigarettes and determining whether brain activity predicts the ability to quit smoking. ■

SCANS SHOW EFFECTS OF CRAVING REGULATION IN THE BRAIN When study participants thought of the long-term negative consequences of cigarette consumption (after receiving the instruction "LATER"), rather than short-term pleasures ("NOW"), they reduced their craving. Brain scans showed increased activity in the dorsolateral prefrontal cortex—a region critical to setting goals, planning, and controlling behavior—which, in turn, inhibited the ventral striatum, part of the reward pathway that generates craving.



SOURCES

Kober, H., et al. Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proceedings of the National Academy of Sciences* 107(33):14811–14816, 2010.

Kober, H., et al. Regulation of craving by cognitive strategies in cigarette smokers. *Drug and Alcohol Dependence* 106(1):52–55, 2010.

Well-Known Mechanism Underlies Benzodiazepines' Addictive Properties

Like opioids and cannabinoids, diazepam and other benzodiazepines take the brakes off activity of dopamine-producing neurons.

BY NIDA NOTES STAFF

Since their introduction in the 1960s, drugs categorized as benzodiazepines, which include diazepam (Valium) and alprazolam (Xanax), have been widely prescribed to treat anxiety and insomnia, alcohol withdrawal, and other conditions. Although they are highly effective for their intended uses, these medications must be prescribed with caution because they can be addictive. Now, work by NIDA-funded researchers has established that benzodiazepines cause addiction in a way similar to that of opioids, cannabinoids, and the club drug gamma-hydroxybutyrate (GHB). The discovery opens the door to designing new benzodiazepines that counteract anxiety but are not addictive.

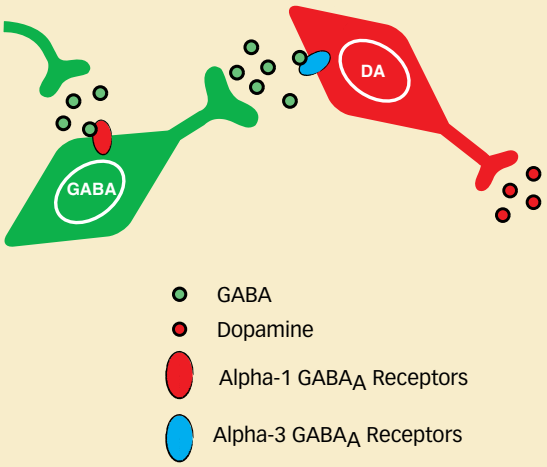
Dr. Christian Lüscher and colleagues at the University of Geneva, Switzerland, studied benzodiazepines as part of a larger project to identify the point of convergence for all neurobiological pathways to drug addiction. Their findings strongly suggest that this juncture occurs when dopamine surges in response to drug taking initiate a change in synaptic plasticity in dopamine-producing cells.

FROM RECEPTOR ACTIVATION TO DOPAMINE SURGE

The pleasurable sensations that make addictive drugs disastrously attractive

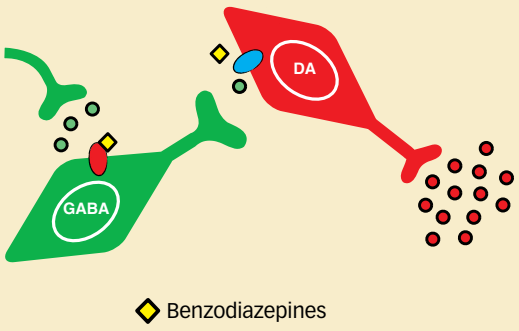
MECHANISMS OF BENZODIAZEPINE ADDICTION

Without Benzodiazepines



Both inhibitory interneurons (labeled GABA) and dopaminergic neurons (labeled DA) are subject to the restraining influence of the inhibitory neurotransmitter GABA. A key difference, however, is that GABA influences the inhibitory interneurons largely via the alpha-1 subset of GABA$_A$ receptors and the dopaminergic neurons largely via the alpha-3 subtype.

With Benzodiazepines



Benzodiazepines currently on the market do not interact strongly with alpha-3 GABA$_A$ receptors on dopaminergic neurons and so have no direct impact on dopamine release. However, the drugs do interact strongly with alpha-1 GABA$_A$ receptors, thereby curtailing inhibitory interneurons' release of GABA into synapses with dopaminergic neurons. The net result is a lessening of GABA restraint on the dopaminergic neurons and an increase in dopamine release.

for vulnerable individuals occur when dopamine levels in the brain's reward area abruptly surge. Researchers had worked out how most addictive drugs, but not benzodiazepines, precipitate these surges.

Dr. Lüscher and colleagues have now demonstrated that benzodiazepines weaken the influence of a group of cells, called inhibitory interneurons, in the brain's ventral tegmental area (VTA). These neurons normally help prevent excessive dopamine levels by down-regulating the firing rates of dopamine-producing neurons. Two negatives make a positive, so when benzodiazepines limit the interneurons' restraining influence, the dopamine-producing neurons release more dopamine.

The Swiss researchers traced benzodiazepines' effect on VTA interneurons to the drugs' activation of a subset of $GABA_A$ (gamma-aminobutyric acid type-A) receptors on the interneurons. Although benzodiazepines typically activate multiple subtypes of $GABA_A$ receptors, their activation of the the alpha-1 subtype is decisive for their impact on VTA interneuron behavior. These interneurons are highly sensitive to such activation because they carry abundant numbers of these receptors. By staining brain tissue, the researchers showed that 81 percent of VTA interneurons carry $GABA_A$ receptors that contain the alpha-1 subunit.

To prove that activation of alpha-1 $GABA_A$ receptors underlies benzodiazepines' dopamine effect, the researchers administered a typical benzodiazepine, midazolam, to two groups of mice. The results supported the researchers' proposed mechanism: In normal animals, the firing rate of interneurons decreased in response to the drug, while that of dopamine-producing neurons increased. In contrast, in animals that were genetically altered to prevent benzodiazepines from potentiating alpha-1 $GABA_A$ receptors, the drug had little or no impact on neuron firing.

A behavioral finding completed the chain of proofs linking benzodiazepines' stimulation of alpha-1 $GABA_A$ receptors to their rewarding effects. When given the option of drinking sugar water or a sweetened solution of midazolam, normal mice imbibed roughly three times as much drug-laced as drug-free liquid. Mice with altered alpha-1 $GABA_A$ receptors, however, drank equal amounts of each, thereby exhibiting no evidence of finding one drink more rewarding than the other.

Dr. Lüscher and colleagues showed that benzodiazepines induce AMPA receptor migration via the alpha-1 $GABA_A$ receptors. In these experiments, brain tissue from normal mice exhibited GluA2-lacking AMPA receptors after a single injection of midazolam, but tissue from mice with benzodiazepine-insensitive alpha-1 $GABA_A$ receptors did not. Recordings of intracellular electrical currents confirmed synaptic changes of dopamine-producing neurons in the normal mice and not the altered mice. To pin down the relationship further, the researchers injected mice with two other compounds, one (zolpidem) that preferentially activates only the alpha-1 $GABA_A$ receptors, and one (L-838417) that antagonizes these receptors. GluA2-lacking AMPA receptors were expressed in dopamine-producing neurons following a treatment with zolpidem, but not with L-838417.

When benzodiazepines limit the interneurons' restraining influence, the dopamine-producing neurons release more dopamine.

Benzodiazepines' newly discovered mechanism for producing reward is comparable to those of opiates, cannabinoids, and GHB. Each of the four drugs reduces an inhibitory influence on dopamine-producing cells, thereby promoting dopamine spikes.

FROM SURGE TO ADDICTION

Dopamine surges are transient events, but addictive drugs cause long-lasting changes in the reward system. Among the earliest of these along the path from voluntary to compulsive drug use and addiction is the migration of certain AMPA receptors (i.e., GluA2-lacking receptors) from the interior to the surface of the dopamine-producing neurons. These receptors render the cell more susceptible to stimulation by the excitatory neurotransmitter glutamate, and as a result, the cells respond to future drug exposures with larger dopamine surges that produce even more intense pleasure. Scientists also have evidence that these special AMPA receptors initiate a series of changes in neural transmission that cumulatively give rise to the range of addictive symptoms.

CONCLUSIVE PROOF

The Swiss researchers hypothesize that although different addictive drugs produce dopamine surges by various mechanisms, the subsequent chain of effects is the same. Consistent with this idea, they showed that even in the absence of any drug, artificial stimulation of the dopamine-producing neurons is sufficient to induce the appearance of GluA2-lacking AMPA receptors.

In this experiment, the researchers introduced a virus containing a light-activated protein, channelrhodopsin, into the dopamine-producing cells of mice. When exposed to light pulses from an optical fiber inserted into the animals' VTA, the channelrhodopsin stimulated neuron firing in bursts similar to those

[*Continued on page 11*]

Physical Activity Reduces Return to Cocaine Seeking in Animal Tests

Exercise also decreases neural change linked with drug seeking during abstinence.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Aerobic exercise might help cocaine abusers establish and maintain abstinence, recent NIDA-funded animal research suggests. In two independent studies, running on an exercise wheel reduced rats' cocaine seeking during forced abstinence and their eagerness to resume cocaine seeking following the abstinence. One study indicated that exercise may produce these effects in part by lowering brain levels of a protein that has been linked to drug craving.

The research teams, one led by Dr. Marilyn Carroll at the University of Minnesota and the other by Dr. Wendy Lynch at the University of Virginia, examined the impact of exercise on drug seeking with a protocol that researchers often use to test potential addiction medications. Their work highlights the potential usefulness of such protocols for assessing behavioral approaches to addiction treatment as well.

EXERCISE

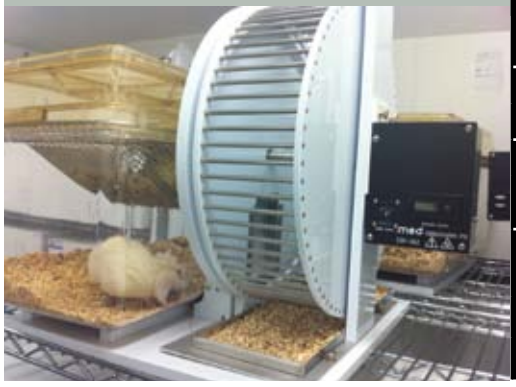
The research teams varied details of the test protocol, but both preserved its basic three-phase structure, which parallels a person's acquisition of chronic drug abuse, establishment of abstinence, and exposure to a relapse trigger:

- Self-administration: The animal self-administers cocaine infusions by pressing a lever, ultimately leveling off at a dosage that it apparently finds optimal.
- Extinction (of the lever-pressing behavior): The researchers deactivate the lever and observe how rapidly the rat tapers off its lever pressing in the absence of the drug reward.
- Reinstatement: The researchers expose the rat to some strong reminder of the rewarding sensations produced by the drug—e.g., a priming dose or drug-associated cues—and observe how avidly the animal resumes lever pressing.

In studies with this protocol, researchers administer a potential treatment after the self-administration phase and judge it to be effective if it results in reduced lever pressing during extinction and/or reinstatement. Hence, the Virginia and Minnesota teams moved their animals to cages with exercise wheels after the self-administration stage (see chart below). Both found that animals that ran on the wheels tapered off lever pressing faster during extinction and took it up less avidly during reinstatement, compared with control animals placed in cages with locked running wheels.

In the Minnesota study, female rats that exercised pressed the lever about half as often, on average, during the first 9 days of the 14-day extinction phase. Dr. Carroll and colleagues also found that exercise

THE EXPERIMENTAL PROTOCOLS Using slightly different procedures, each team combined standard drug self-administration and reinstatement procedures—an animal model of relapse—with access to a running wheel to investigate whether exercise reduces cocaine seeking.



TEAM	CARROLL	LYNCH
SEX OF RATS	Female	Male
TRAINING IN RUNNING WHEEL	6 hours daily for 8 days	None
SELF-ADMINISTRATION IN ABSENCE OF WHEEL (LEVER DELIVERS COCAINE)	6 hours daily for 10 days	24-hour access for 10 days
FORCED ABSTINENCE (NO LEVER, NO COCAINE)	None	2 hours daily for 14 days Wheel or Locked Wheel
EXTINCTION (LEVER NO LONGER DELIVERS COCAINE)	6 hours daily for 14 days Wheel or Locked Wheel	6 to 8 sessions, 1 hour each
REINSTATEMENT AFTER TRIGGER (LEVER NO LONGER DELIVERS COCAINE)	Single 6-hour test Trigger = Priming injection Wheel or Locked Wheel	Single 1-hour test immediately after extinction session Trigger = Drug-associated cues

reduced lever pressing during reinstatement when animals ran on the same day that they received a priming dose of cocaine, but not when there was a delay between receiving the priming dose and being introduced to the wheel.

In the Virginia study, male rats that exercised for up to 2 hours a day during a 2-week period of forced abstinence between self-administration and extinction pressed the lever about 35 percent less often during the extinction phase and about 45 percent less often during reinstatement.

DECREASED NEUROADAPTATION

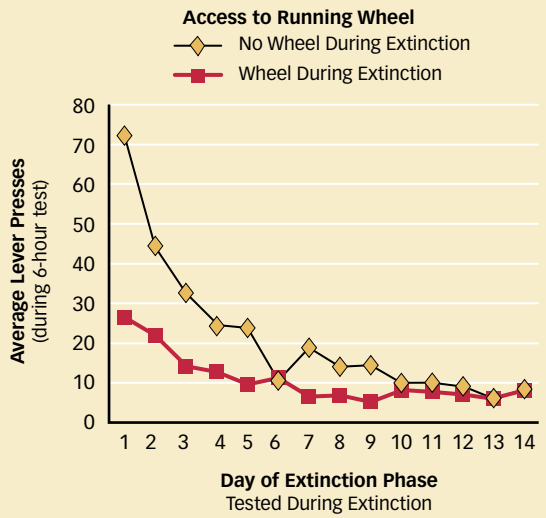
Both studies indicate that exercise does more than simply provide an alternative activity that reduces the time available for drug seeking, the researchers say. The researchers note that both exercise and addictive drugs raise levels of dopamine in the brain's reward system, and as a result, exercise may compete with cocaine as a source of pleasurable sensations. In addition, the Virginia researchers found evidence suggesting that exercise may alter levels of the neurotransmitter glutamate in their rats' prefrontal cortex (PFC). Such an effect might weaken the progressive intensification (incubation) of craving that takes place during early abstinence from cocaine and appears to depend largely on glutamate.

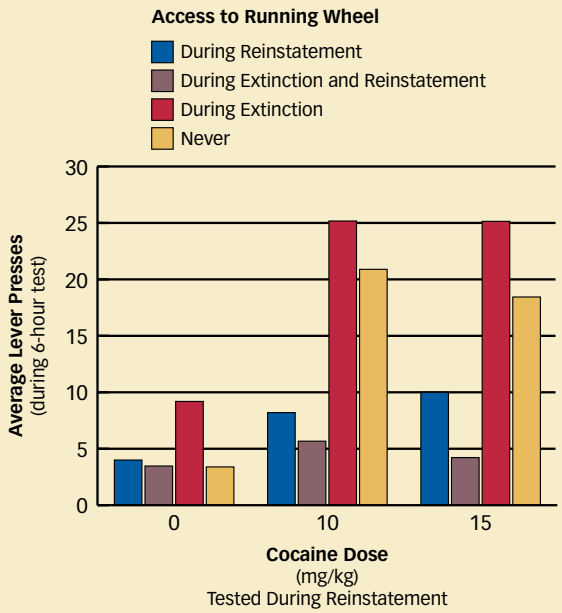
Dr. Lynch and colleagues assayed brain tissue from the PFC of their animals 1 day after the end of reinstatement. Exercise was associated with 32- and 42-percent reductions in the activity of two proteins, extracellular signal-regulated kinase (ERK) 1 and 2, whose levels are regulated by both dopamine and glutamate. Previous research has established associations between ERK, drug-seeking behavior, and the incubation of cocaine craving.

Dr. Lynch and colleagues continue to investigate whether exercise counters changes in glutamate neurotransmission and other neuroadaptations that characterize the transition from drug abuse to addiction (see "Medications That Normalize Brain Glutamate Reduce Drug Seeking in Rats," *NIDA Notes*, Volume 23, Number 2, page 1). Dr. Carroll and colleagues are exploring the relationships among propensity for wheel running, neuronal activity in the brain's reward pathway, and subsequent levels of cocaine self-administration (see box, page 11).

"These studies are valuable because they establish a causal link between exercise and a decrease in drug-seeking behavior and demonstrate two independent mechanisms by which this may be achieved," says Dr. Mark Smith of Davidson College, a researcher on exercise and drug abuse who was not affiliated with either study. "Dr. Carroll's

ACTIVITY REDUCES RATS' RETURN TO COCAINE In a study at the University of Minnesota, female rats that had access to a functional running wheel during extinction pressed the cocaine-delivery lever less often during this period than rats that did not have such access (left-hand graph). In response to a priming injection of the drug, rats that had access to a running wheel during reinstatement pressed the cocaine-delivery lever less often at this stage than rats with a locked wheel or access to a running wheel only during extinction (right-hand graph).





Propensity for Wheel Running Linked to Response to Drugs

Prior research led by Dr. Marilyn Carroll at the University of Minnesota, a pioneer in the behavioral study of exercise as a treatment for drug abuse, found that among female—but not male—rats, the propensity for wheel running was related to substance abuse vulnerability. Animals that ran avidly before drug exposure went on to self-administer more cocaine than rats that ran less. They also sought cocaine more during reinstatement compared with those that had been less active prior to drug exposure. Researchers studying the impact of exercise on addiction processes, therefore, must ensure that propensity for wheel running does not influence their results. Dr. Carroll and others have also demonstrated relationships between some other behavioral characteristics—e.g., novelty seeking and high intake of saccharine—and increased drug self-administration.

Source: *Pharmacology, Biochemistry and Behavior* 82(3):590–600, 2005.

team showed that exercise functions as an alternative, nondrug reinforcer that decreases reinstatement, and Dr. Lynch's team demonstrated that exercise mitigates the neurobiological consequences of cocaine self-administration that contribute to relapse. Both studies' findings support the expanded use of exercise-based interventions in substance abuse treatment programs," he says.

Drs. Carroll and Lynch agree that including exercise as an adjunct to residential substance abuse treatment is a good idea. "Patients in substance abuse treatment would probably need incentives to encourage exercise as an alternative behavior, but our research suggests that access to activity might help," says Dr. Carroll.

Although research has not directly demonstrated that adding exercise to addiction treatment helps prevent relapse, results from extant clinical studies—mostly on smoking cessation—are promising. "The health benefits of exercise warrant inclusion in treatment, in addition to the potential benefits in relapse prevention," says Dr. Lynch.

"An important question for future research is what aspect of locomotor activity is protective against drug taking or drug seeking?" says Dr. Cora Lee Wetherington of NIDA's Division of Basic Neuroscience and Behavioral Research. Researchers need to identify the timing, extent, and other characteristics of locomotor activity (e.g, calorie expenditure) that might facilitate reductions in drug-related behaviors, she adds.

The protocols used in the Minnesota and Virginia studies will help scientists address these issues. "These studies are a testament to the importance of animal models that combine behavioral and environmental factors related to drug abuse, which then allow researchers to investigate the underlying neurobiology," says Dr. Wetherington. ■

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[*Continued from page 8*]

produced by addictive drugs. The result was an increase in GluA2-lacking AMPA receptors comparable to that seen following exposure to addictive drugs.

"This was a nail-in-the-coffin study to show that activity of dopaminergic neurons leads to synaptic adaptation that is involved in addiction," says Dr. Lüscher. "This is why addiction is so difficult to treat. Even if you clear the drug from the body, there are long-lasting changes in brain architecture."

TOWARD BETTER BENZODIAZEPINES

Taken together, the data from the studies show that the activation of alpha-1-containing $GABA_A$ receptors by benzodiazepines calms inhibitory interneurons, increasing dopaminergic neuron firing, and leads to the strengthening of excitatory synapses that favor addictions. Dr. Roger Sorensen of NIDA's Functional Neuroscience Research Branch says, "This is the first demonstration that acute benzodiazepine use can increase dopamine release, supporting its addictive potential."

"Now that we know that it's the alpha-1-containing $GABA_A$ receptor that is responsible for benzodiazepine addiction, we can design benzodiazepines that do not touch those particular receptors," says Dr. Lüscher. Drugs that bind only to alpha-2-containing $GABA_A$ receptors, he adds, might relieve anxiety nonaddictively. "Such substances already exist for research purposes," Dr. Lüscher says. "It's possible that we can also create them for clinical use." ■

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Home Visits by Nurses to Low-Income First-Time Mothers Yield Enduring Benefits

Savings on welfare-related outlays offset the cost of a program that improved children's health and school outcomes over 12 years.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Home visits by nurses to low-income first-time mothers, starting during pregnancy and extending into the second year of their children's lives, have a positive and long-lasting impact on families. The latest findings, by Dr. David Olds and colleagues at the University of Colorado-Denver, indicate that the Nurse-Family Partnership (NFP) program improves outcomes for mothers and children 10 years after its administration and saves the government money. The benefits of the program—now documented among three groups of low-income mothers and children—have led to the expansion of government funding and technical support for states to deliver the intervention.

HELP AT THE START

During 1990 and 1991, Dr. Olds and colleagues recruited 743 low-income pregnant women in Memphis, Tennessee, and randomly assigned them to the NFP or a control group. All the women were about to become mothers for the first time, all but a few were African-American, about two-thirds were teens, and most were unmarried.

The women in both groups received free transportation for scheduled prenatal care, as well as developmental screenings and referrals for their children at ages 6 months, 12 months, and 24 months. Women assigned to the NFP program also received home visits from a nurse—on average, seven visits prior to giving birth and 26 visits during the child's first 2 years.

The visiting nurses used program guidelines designed to improve the women's health practices relevant to birth outcomes, bolster parents' caregiving attitudes and expand their skills, and encourage parents to enhance their own life-course development. In addition to giving practical advice on pregnancy and child care, the nurses guided the mothers toward healthy decisions—for example, completing their own educations, getting into the work force, and making good choices about their next pregnancy.

THE NURSE CONNECTION A 17-year old first-time mother in the program says, "When I was pregnant, I felt I didn't have anybody to lean on. I was so lucky to have a nurse like her."

TEN YEARS LATER

The researchers contacted and interviewed 594 of the mothers and 578 of their children when the children were 12 years old. At this assessment, the NFP mothers reported greater sense of mastery over the challenges of living and rearing their children. None of the NFP mothers reported that alcohol or other drug use impaired her functioning at work or home, compared with 2.5 percent among those in the control group. The nurse-visited mothers also reported longer relationships with current partners—averaging 60 months versus 53 months for women in the control group.

At 12 years of age, fewer NFP children than control children reported having used cigarettes, alcohol, or marijuana during the past 30 days (1.7 percent versus 5.1 percent). Although these percentages are small, the potential impact of the threefold difference is great because children who begin using substances at such an early age have a high risk of becoming dependent on them. The NFP children also reported less clinical or near-clinical anxiety and depression than the controls (22 percent versus 31 percent). Among those children whose mothers had low "psychological resources" (such as problems with depression or anxiety or low confidence that they could manage challenges), the NFP children's reading and

math scores were higher than those of the control group throughout the first through the sixth grades.

PROGRAM COSTS OFFSET

The cost of NFP nurse training, visits, and program administration averaged $11,511 per family (all monetary figures are in 2006 dollars and discounted at 3 percent per year). Over the years of services and followup, the government spent $12,300 less per NFP family compared with that spent per control family on food stamps, Medicaid, Aid to Families with Dependent Children, and Temporary Assistance for Needy Families. The net saving of roughly $800 per NFP family does not take into account potential reduced medical, social service, and other costs related to the children's improved outcomes. If the NFP pattern of benefits continues, the bulk of such savings will accrue during the children's late adolescence, when their risks for drug abuse, neuropsychiatric illness, and criminal justice involvement are greatest.

Dr. Olds and colleagues hypothesize that the NFP women reduced their need for government aid by spacing their subsequent pregnancies more widely and through the increased stability of their partner relationships. The researchers note, however, that one anticipated source of reduced welfare-related costs did not materialize: Counter to expectations, over the entire followup period, the NFP mothers did not have higher employment rates than the controls.

ACTIVATING PARENTAL INSTINCTS

Dr. Olds says the NFP program helps children primarily through its effects on mothers' decisionmaking and confidence. The decisions mothers make early on, and their resourcefulness in implementing them, have a long-term influence on the family environment, improving children's ability to control their behavior and boosting academic achievement. "The nurses in the program listen to parents, support them, and help channel parents' instinctual drives to protect and support their children," says Dr. Olds.

Dr. Olds and colleagues plan to assess the Memphis children at age 18 to determine whether NFP participation influences substance abuse, criminal justice involvement, HIV risk behaviors, educational achievement, and other outcomes at that age. To date, the researchers have examined only first-born children, but in future work, they plan to test whether younger siblings also benefit. If other children in the family gain advantages from the NFP, then the savings to the government will be greater.

The Memphis findings accord well with those of other NFP studies. Dr. Olds and colleagues found lower rates of criminal justice involvement, teen motherhood, and Medicaid use among the daughters of participants in the initial NFP intervention at age 19—mostly white, unmarried, and low-income pregnant women recruited in Elmira, New York, from 1978 to 1980—compared with a control group. Families from the most recent NFP cohort of women recruited in Denver, Colorado, during 1994 and 1995, about half of whom are Latina, have also benefited from the program. At age 4, NFP children born to mothers with low psychological resources showed better language skills and execu-

"The nurses in the program listen to parents, support them, and help channel parents' instinctual drives to protect and support their children."

– Dr. David Olds

NURSE-FAMILY PARTNERSHIP YIELDS LASTING BENEFITS Home visits by nurses to low-income first-time mothers, starting during pregnancy and extending into the second year of the children's lives, had a positive impact on children at age 12. Children whose mothers were depressed and anxious demonstrated the greatest academic benefits from the program.

OUTCOME FOR CHILDREN	NURSE-FAMILY PARTNERSHIP GROUP	CONTROL GROUP
Percent used cigarettes, alcohol, or marijuana during past 30 days	1.70	5.10
Number of substances used during past 30 days	0.02	0.08
Number of days of substance use during past 30 days	0.03	0.18
Self-reported anxiety and depression	22.10	30.90
Reading and math scores on standardized tests*	88.78	85.70
Reading and math grade point average (grades 1–6)*	2.46	2.27
Percentile on reading and math group achievement tests (grades 1–6)*	40.52	34.85

* Among children whose mothers were below the median for psychological resources, experiencing depression and anxiety, and with low intellectual functioning and little confidence that they could handle challenges.

tive function, such as planning and behavioral control, than their counterparts in the comparison group.

Overall, findings from the NFP trials show that early interventions with low-income families can yield long-term benefits and economic advantages. Dr. Olds notes, in particular, that the NFP was effective for families who lived in Memphis neighborhoods with high levels of poverty, unemployment, single-parent homes, and racial segregation. Moreover, during the study, these communities also experienced policy and economic shifts that influenced families' opportunities and well-being—including welfare reform and periods of economic boom and bust.

Dr. Leslie Leve of the Oregon Social Learning Center, a prevention researcher not affiliated with the study, says, "The enduring benefits of NFP to families are impressive, and the cost savings produced by the program further showcase the high value that can come from preventive services delivered at the point when a young family is first identified as possibly being at risk but isn't yet showing signs of failure, rather than waiting to provide support until a child has dropped out of school or has started using drugs."

Dr. Belinda Sims of NIDA's Division of Epidemiology, Services and Prevention Research agrees that the cost information so far available on the program is promising, and she adds that followup of children into adolescence is a critical component of the research. "The NFP addresses family-level risk factors, such as low resources and high stress, and assists families by getting mothers to prenatal care visits during pregnancy and getting children to well-baby visits in the first 2 years of life, and by linking families to resources in the community," she says. "In this way, the intervention seems to help families put children on a positive developmental path so that they have less risk for drug abuse later." ■

THE GIFT OF CONFIDENCE The fiancé of a woman who received pre- and postnatal nursing visits says, "We're doing okay! We can actually say we're going to make it."

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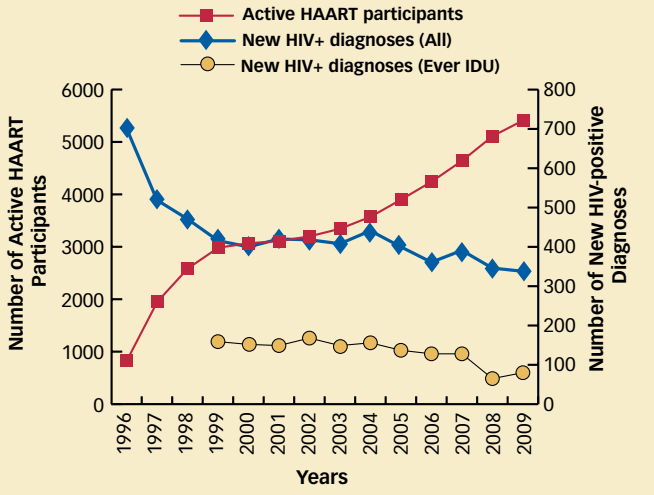
Antiretroviral Treatment Reduces Spread of HIV Among Injection Drug Users

Highly active antiretroviral therapy (HAART) not only benefits the health of individuals with HIV and a history of injection drug use but also reduces transmission of the virus to others in the community. Using province-wide data from British Columbia from 1996 to 2009, NIDA-funded researchers found a strong association between more extensive treatment with HAART and reductions in new HIV diagnoses per year, as well as decreased viral load in patients.

During the study period, as the province expanded HAART coverage more than five-fold as part of its universal health care program, new HIV diagnoses decreased about 50 percent, says lead investigator Dr. Julio Montaner of the British Columbia Centre for Excellence in HIV/AIDS in Canada. The increase in the number of people receiving HAART during the last 5 years of the study was accompanied by a greater decrease in new HIV cases among those with histories of illicit injection drug use than among those with no such history.

The researchers conclude that HAART treatment, which has already been demonstrated to dramatically reduce mother-to-child and sexual transmission of HIV, also markedly reduces HIV transmission among people who have a history of illicit injection drug use. In prior research, the team found that mortality rates from HIV after receiving HAART were comparable among people who used illicit injection drugs and those who did not (see "Study Gives Green Light to Antiretroviral Medications for HIV-Infected Injection Drug Users," *NIDA Notes*, Volume 22, Number 6, page 6).

TREATMENT EXPANSION PARALLELS DROP IN NEW HIV CASES AMONG INJECTION DRUG USERS As British Columbia extended highly active antiretroviral therapy (HAART), the number of new HIV diagnoses fell. A reduction was seen among individuals who had a history of illicit injection drug use (IDU) as well as in the general population.



The Lancet 376(9740):532–539, 2010.

Vouchers Improve Mothers' Smoking Abstinence and Newborns' Weights

Voucher payments for not smoking during pregnancy help women to stop using tobacco and boost the growth of their infants, according to an analysis of data from three controlled trials by Dr. Stephen Higgins and colleagues at the University of Vermont. About 34 percent of 85 women who participated in voucher-based reinforcement therapy (VBRT) were abstinent, as verified by urine tests, during late pregnancy compared with 7 percent of 81 women in the comparison group, who earned vouchers for attending assessments regardless of quitting success. Intervention participants maintained an advantage 3 months after giving birth: 24 percent were abstinent compared with only 3 percent of the control group.

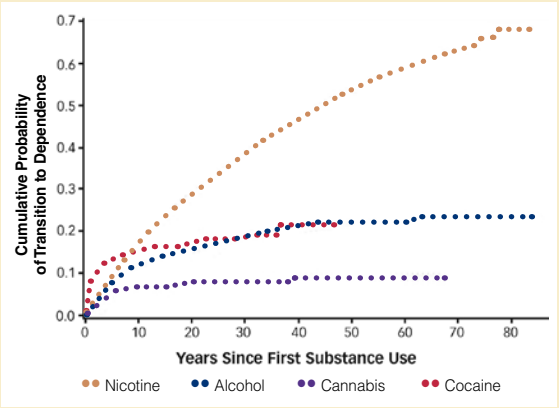
The babies born to women who participated in the intervention showed benefits in newborn weight, which affects immediate and longer term health risks. About 6 percent of women in the VBRT group had a baby categorized as low birth weight—less than 2,500 grams—compared with 19 percent of those in the control group. Infants born to women in the VBRT group weighed 202 grams more, on average, than those from control-group mothers.

All the women who participated in the trials received advice and encouragement to quit smoking from their obstetricians. The participants, most of whom had low incomes, each received, in total, vouchers worth about $450. The findings extend the Vermont team's prior results that VBRT for smoking cessation improves fetal growth (see "Vouchers Boost Smoking Abstinence During Pregnancy," *NIDA Notes*, Volume 23, Number 1, page 10).

Addiction 105(11):2023–2030, 2010.

WHAT THE NUMBERS SAY

Tobacco Smokers Have High Probability of Transition to Dependence



First-time smokers have a 68 percent chance of sooner or later becoming nicotine dependent, according to a recent estimate based on national survey data. The probability of first-time alcohol, cocaine, and cannabis users transitioning to dependence was much less. For cocaine and cannabis, about half of the eventual cases of dependency occurred within 4 and 5 years, respectively, after first use. For alcohol and nicotine, half of the dependencies developed in 13 and 27 years, respectively. Estimates were based on self-report data from 15,918 nicotine, 28,907 alcohol, 7,389 cannabis, and 2,259 cocaine users who participated in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

Source: Lopez-Quintero, C., et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug and Alcohol Dependence* 115(1-2):120–130, 2011.

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